SUSTAINED RELEASE PHARMACEUTICAL DOSAGE FORMS WITH MINIMIZED PH DEPENDENT DISSOLUTION PROFILES

This invention relates to pharmaceutical compositions. More particularly, this invention relates to pharmaceutical compositions having a pH-independent or a minimized pH-dependent dissolution profile. In particular, such composition includes at least one pharmaceutically active agent that has a pH dependent solubility profile, at least one non-pH-dependent sustained release agent, and at least one pH-dependent agent that increases the dissolution rate of the at least one pharmaceutically active agent at a pH in excess of 5.5. The active agent(s) has (have) a solubility profile wherein the active agent(s) is (are) more soluble in an acidic medium than in a basic medium.

The rate at which a drug goes into solution when it is dissolved in a medium is proportional to the solubility of the drug in the medium. Many drugs have different solubilities at different pHs. These pH-dependent solubility differences lead to pH-dependent dissolution profiles. In general, pH-dependent dissolution is an undesirable product characteristic.

Compressed matrix tablets containing a basic drug often give a faster dissolution profile in simulated gastric fluid, having a pH about 1.0, than in simulated intestinal fluid (pH 6.8 to 7.4).

It is an object of the present invention to provide a pharmaceutical composition with a minimized pH dependent or a pH-independent dissolution profile.

In accordance with an aspect of the present invention, there is provided a pharmaceutical composition. The composition comprises at least one pharmaceutically active agent that is pH dependent, at least one non-pH dependent sustained release agent, and at least one pH-dependent agent that increases the rate of release of the at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5, such as at least one organic acid that maintains an acidic micro-environment in the tablet.

Pharmaceutically active agents which are pH dependent and which may be included in the composition include, but are not limited to, weakly basic drugs and their salts that have higher solubilities at lower pH levels. Such drugs include, but are not limited to, guanfacine hydrochloride, guanadrel sulfate, reserpine, anagrelide hydrochloride, propanolol, metoprolol, atenolol, timolol, erthyrthromycin, clonidine, chlorpheniramine, bromopheniramine, diltiazen, and scopolamine. In general, the pharmaceutically active agent is present in the composition in an amount of from about 0.1 wt, % to about 70 wt. %, preferably from about 1 wt. % to about 40 wt %. In one embodiment, the at least one pharmaceutically active agent is guanfacine hydrochloride. In another embodiment, the at least one pharmaceutically active agent is anagrelide hydrocholoride. It is to be understood, however, that the scope of the present invention is not to be limited to any particular pharmaceutically active agent.

Non-pH-dependent sustained release agents which may be included in the composition include, but are not limited to, ethylcellulose, cellulose acetate, vinyl acetate/vinyl chloride copolymers, acrylate/methacrylate copolymers, polyethylene oxide, hydroxypropyl methylcellulose, carrageenan, alginic acid and salts thereof, hydroxyethyl cellulose, hydroxypropyl cellulose, karaya gum, acacia gum, tragacanth gum, locust bean gum, guar gum, sodium carboxymethyl cellulose, methyl cellulose, beeswax, carnauba wax, cetyl alcohol, hydrogenated vegetable oils, and stearyl alcohol. In general, the at least one non-pH-dependent sustained release agent is present in the composition in an amount of from about 5 wt. % to about 50 wt. %, preferably from about 10 wt. % to about 30 wt. %. It is to be understood, however, that the scope of the present invention is not to be limited to any particular non-pH-dependent sustained release agents.

pH-dependent agents that increase the rate of release of the at least one pharmaceutically active agent from the tablet at a pH in excess of 5.5 include, but are not limited to, polymers that swell at a pH in excess of 5.5, and enteric agents, and/or agents that increase the solubility of the at least one pharmaceutically active agent at a pH greater than 5.5, by maintaining an acidic microenvironment in the tablet, e.g., an organic acid. The at least one pH-dependent agent is present in the composition in an amount of from about 0.5 wt. % to about 40 wt. %, preferably from about 1 wt. % to about 20 wt. %.

Polymers that swell at a pH in excess of 5.5 include, but are not limited to, acrylic acid copolymers, sodium alginate, carrageenan, alginic acid, pectin, and sodium carboxymethyl cellulose.

Enteric agents include, but are not limited to, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, methacrylic acid coplymers, cellulose acetate trimellitate, hydroxypropyl methylcellulose acetate, succinate, shellac, and zein.

Agents that increase the solubility of the at least one pharmaceutically active agent at a pH greater than 5.5 include, but are not limited to, organic acids. Such organic acids maintain an acidic microenvironment in the tablet, and include, but are not limited to, citric acid, fumaric acid, tartaric acid, adipic acid, glucono delta-lactone, and malic acid.

The composition of the present invention may further include other materials such as bulking agents, disintegrating agents, anti-adherants and glidants, lubricants, and binding agents.

Bulking agents include, but are not limited to, microcrystalline cellulose (eg., Avicel®, FMC Corp., Emcocel®, Mendell Inc.), mannitol, xylitol, dicalcium phosphate (eg. Emcompress, Mendell Inc.) calcium sulfate (eg. Compactrol, Mendell Inc.) starches, lactose, sucrose (Dipac, Amstar, and Nutab, Ingredient Technology), dextrose (Emdex, Mendell, Inc.), sorbitol, cellulose powder (Elcema, Degussa, and Solka Floc, Mendell, Inc.) The bulking agent may be present in the composition in an amount of from about 5 wt. % to about 90 wt. %, preferably from about 10 wt. % to about 50 wt. %.

Disintegrating agents which may be included in the composition include, but are not limited to, microcrystalline cellulose, starches, crospovidone (eg. Polyplasdone XL, International Specialty Products.), sodium starch glycolate (Explotab, Mendell Inc.), and crosscarmellose sodium (eg., Ac-Di-Sol, FMC Corp.). The disintegrating agent may be present in the composition in an amount of from about 0.5 wt. % to about 30 wt %, preferably from about 1 wt. % to about 15 wt. %.

Antiadherants and glidants which may be employed in the composition include, but are not limited to, talc, corn starch, silicon dioxide, sodium lauryl sulfate, and metallic stearates. The antiadherant or glidant may be present in the composition in an amount of from about 0.2 wt. % to about 15 wt. %, preferably from about 0.5 wt. % to about 5 wt. %.

Lubricants which may be employed in the composition include, but are not limited to, magnesium stearate, calcium stearate, sodium stearate, stearic acid, sodium stearyl